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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,481	07/09/2001	Stephen Mayo	A-70586-1/RFT/RMS/RMK	5918

7590 06/30/2004

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,481	MAYO ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/30/04 has been entered.

2. Claims 40-49 are pending and examination.

3. Claim 49 is objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim (claims 43 and 44).

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 45-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 45-48 are indefinite because it is unclear whether the non-naturally occurring integrin protein would comprise the specific substitutions of SEQ ID NO: 1 *and* the specific SEQ ID NO: or the specific substitutions of SEQ ID NO: 1 *or* specific SEQ ID NO:. The specific SEQ ID NOs contain the specific recited substitutions but lack the first 16 amino acid of SEQ ID NO: 1.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 40-44 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-naturally occurring integrin protein comprising the F156L, V160I, V199I, I215L, V238F, V239L, I240L, A259L, I269L, V271F, I287V, V299A and I308V substitutions (as set forth in SEQ ID NO: 3 (ido1q)), the F156W, V199I, I215L, V238F, V239L, I240L, A259L, I287V and V299I substitutions (as set forth in SEQ ID NO:4 (ido1r)) or I139V, M153A, V157I, V199I, V238I, V239L, I287V and V299I substitutions (as set forth in SEQ ID NO 5 (ido2r)) as compared to the human integrin protein of SEQ ID NO:1 for stabilizing the integrin I domain in the open conformation and I215V, V219I, F223L, and V238I

as compared to the human integrin protein of SEQ ID NO:1 (as set forth in SEQ ID NO: 6 (jlm2r)) for close conformation, and a composition thereof does not reasonably provide **enablement** for any non-naturally occurring integrin protein comprising 4 or more amino acid substitutions as compared to the human integrin protein of SEQ ID NO: 1, said substitutions selected from the group of amino acid residues consisting of residues 139, 154, 156, 157, 160, 199, 215, 219, 223, 338, 239, 240, 259, 269, 271, 287, 299 an d308 in claim 40, the non-naturally occurring integrin protein wherein said substitutions are selected from the group of substitutions consisting of I139V, M153A, F1 561, F156W, V157I, V1601, V199l, 1215L, l215V, V2l9l, F223I., V23817,V2381, V239L, I240L, A259L, 1269L, V271F, I287V, V299A, V2991, and I308V in claim 41, wherein said non-naturally occurring integrin is artificially biased to exist in the open/closed conformation, and wherein said artificial bias is the result of noncontiguous alterations of said protein in claims 23-44, the non-naturally occurring integrin protein, A pharmaceutical composition comprising a non-naturally occurring integrin protein according to any one of the preceding claims and a pharmaceutical carrier in claim 49. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 1/2/04.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The instant claims encompass in their breadth any non-naturally occurring integrin protein that artificially biased to exist in the "open conformation" in claim 43 or "closed conformation permeability activity" in claim 44. However, these configurations are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct *artificially biased structure* to accomplish these mutually exclusive endpoints. The skilled artisan would not have a reasonable expectation that the same substitutions that produce open conformation would also serve to produce closed conformation in the same human integrin protein of SEQ ID NO:1.

There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would use the multifunctional non-naturally occurring integrin protein comprising the specific substitutions as recited in the instant claims. Due to the contradictory and seemingly mutually exclusive results, undue experimentation would be required of the skilled artisan to determine whether the claimed substitutions would result in an open or closed conformation in view of the instant disclosure. Further, there is insufficient evidence or nexus that would lead the skilled artisan to predict the ability of such substitutions to exist in either open or closed conformation.

The specification discloses only four species (3 with open conformation and one with closed conformation), yet claims any non-naturally occurring integrin protein comprising 4 or more amino acid substitutions. Besides, SEQ ID NOs: 3-6, applicant has provided little or no guidance beyond the mere presentation of amino acid positions (those that resulted in SEQ ID NOs: 3-6, see table 1) to enable one of ordinary skill in the art to determine, without undue experimentation, the substitutions in the integrin protein, which lead to the open/closed

conformation, and the nature and extent of the substitutions that can be made in these positions. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims (18 different positions with 20 different amino acid substitutions and combination thereof), and to determine the specific conformation of the infinite variants, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence and the functional properties of the different parts of the protein. Therefore, one skilled in the art at the time of the invention would not be able to predict which substitutions such as the one recited in claim 41 will produce an artificially biased configurations that exist in the open/closed conformation. Consequently the skilled artisan would not know how to use the instant invention as broadly claimed. While experimental testing techniques using monoclonal antibody CBRM1/5 that binds to the I Domain that undergoes shape-shifting (open conformation) and ligand binding to iC3b are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

While the specification on page 71 identifies computational details, potential functions and methods for defining core residues that might work, these descriptions, without more precise guidelines amount to little more than, "a starting point, a direction for further research." *Genentec, Inc. V. Novo Nordisk* A/S, 108 F.3d 1361, 1366, 42 U.S. PQ.2d (BNA) 1001, 1005 (Fed. Cir. 1997).

Still at issue is whether or not the claimed composition would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

In view of the lack of sufficient guidance in the specification and a limited number of working examples, the unpredictability in the art and the breadth of the claims it would take an undue amount of experimentation for one skilled in the art to practice the invention as claimed.

Applicant's arguments, filed 4/30/04, have been fully considered, but have not been found persuasive.

Applicant submits that the specified residues at which amino acid substitutions can occur, methods of making and testing the resulting variants are described throughout the specification.

While Table 1 provides the specific claimed residues as applies to SEQ ID NO: 3-6, wherein SEQ ID NO: 3-5 exist in open conformation and SEQ ID NO:6 exist in closed conformation. However, the specification and table 1 fail to provide guidance as to which 4 or more amino acid substations of the specific residues would lead to artificially biased structure of integrin protein of SEQ ID NO:1 that would exist in either the open or closed conformation. Further, claim 40 recites any amino acid substitution at the specific residues can lead to artificially biased structure in either the open or closed conformation, however no such showing are disclosed in the specification.

8. Claims 40-44 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 1/2/04.

Applicant is in possession of a non-naturally occurring integrin protein comprising the F156L, V160I, V199I, I215L, V238F, V239L, I240L, A259L, I269L, V271F, I287V, V299A and I308V substitutions (as set forth in SEQ ID NO: 3 (ido1q)), the F156W, V199I, I215L, V238F, V239L, I240L, A259L, I287V and V299I substitutions (as set forth in SEQ ID NO:4 (ido1r)) or I139V, M153A, V157I, V199I, V238I, V239L, I287V and V299I substitutions (as set forth in SEQ ID NO 5 (ido2r)) as compared to the human integrin protein of SEQ ID NO:1 for stabilizing the integrin I domain in the open conformation and I215V, V219I, F223L, and V238I as compared to the human integrin protein of SEQ ID NO:1 (as set forth in SEQ ID NO: 6 (jlm2r)) for close conformation, and a composition thereof.

Applicant is not in possession of any non-naturally occurring integrin protein comprising 4 or more amino acid substitutions as compared to the human integrin protein of SEQ ID NO: 1, said substitutions selected from the group of amino acid residues consisting of residues 139, 154, 156, 157, 160, 199, 215, 219, 223, 338, 239, 240, 259, 269, 271, 287, 299 an d308 in claim 40, the non-naturally occurring integrin protein wherein said substitutions are selected from the group of substitutions consisting of I139V, M153A, F1 561, F156W, V157I, V1601, V199l, 1215L, l215V, V2l9l, F223I., V23817,V2381, V239L, I240L, A259L, 1269L, V271F, I287V, V299A, V2991, and I308V in claim 41, wherein said non-naturally occurring integrin is artificially biased to exist in the open/closed conformation, and wherein said artificial bias is the result of noncontiguous alterations of said protein in claims 23-44, the non-naturally occurring integrin protein, A pharmaceutical composition comprising a non-naturally occurring integrin protein according to any one of the preceding claims and a pharmaceutical carrier in claim 49.

Applicant's arguments, filed 4/30/04, have been fully considered, but have not been found persuasive.

Applicant submits that the specified residues at which amino acid substitutions can occur, methods of making and testing the resulting variants are described throughout the specification. Applicant submits that a person skill in the art could envisage the genus of variants as disclosed in claims 40-49.

However, neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (artificially biased to exist in closed/open conformation) to describe the claimed genus, nor does it provide a description of structural features that are common to species (artificially biased integrin protein) The specification provides no structural description of open/closed conformations other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed artificially biased open/closed conformation looks like. The specification's disclosure is inadequate to describe the claimed genus of artificially biased integrin protein.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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